## REMARKS

Claims 1, 2, 4-22, and 25-35 are pending in this application. Claim 17-22 have been withdrawn from consideration by the Examiner.

Claims 5-16 and 26-28 have been amended to more clearly present Applicants' invention. No new matter has been added by the amendments.

### I. The Rejection of Claims 1-2, 4-11, 16 and 28-29, Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 1-2, 4-11, 16 and 28-29 are rejected under 35 U.S.C. 103(a) as allegedly obvious over U.S. Patent No. 5,705,366 to Backus *et al.* ("Backus") in view of Bustin *et al., Journal of Molecular Endocrinology*, 2000, vol. 25, p. 169-193 ("Bustin") and further in view U.S. Patent No. 5,773,258 to Birch *et al.* ("Birch").

According to the Office Action, Backus discloses a method for the coamplification of two or more target nucleic acids having different sequence compositions. The Office Action concedes, however, that Bakus does not disclose the use of a chemically-modified thermostable DNA polymerase. The Office Action attempts to cure this deficiency with the disclosure of Birch, suggesting that Birch discloses the use of a Hot Start DNA polymerase.

The Office Action further concedes that "neither Backus nor Birch explicitly teach that the two or more target nucleic acids are present in comparable copy numbers and the highest copy number is 10 fold." Office Action at page 10, first full paragraph. However, the Examiner argues that Bustin discloses, "the coamplification of nucleic acids which are present at comparable copy numbers, wherein the maximum difference between the lowest and highest copy number is 10-fold . . . ." *Id.* at fourth full paragraph.

The Office Action concludes that, "one of ordinary skill in the art at the time the invention was made would have been motivated to extend the coamplification in the presence of a polymeric volume exclusion agent taught by Backus to incorporate the teachings of Bustin with a reasonable expectation for success in order to achieve quantitative coamplification of two nucleic acid targets of similar copy number." *Id.* at paragraph bridging pages 11-12.

Applicants respectfully disagree and traverse this rejection for at least the following reasons.

Even if the Office were to have made a *prima facie* case of obviousness (which Applicants do not concede that it has), the presently claimed methods provide results that are unexpectedly superior to those that could have reasonably been expected. A *prima facie* showing of obviousness may be rebutted by demonstrating "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

As discussed in the 2002 multiplex PCR review article by Markoulatos *et al.* in *Journal of Clinical Laboratory Analysis 16*:47–51 (2002) ("Markoulatos"), the authors indicated that "common problems encountered in multiplex PCR [are] spurious amplification products, uneven or no amplification of some target sequences, and difficulties in reproducing some results . . . ." Markoulatos at Abstract. As such, the authors cautioned that "development of an efficient multiplex PCR usually requires strategic planning and multiple attempts to optimize reaction conditions." *Id.* Markoulatos further indicates that:

> the relative concentration of the primers, concentration of the PCR buffer, balance between the magnesium chloride and deoxynucleotide concentrations, cycling temperatures, and amount of template DNA and Taq DNA polymerase are important. An optimal combination of annealing temperature and buffer concentration is *essential* in multiplex PCR to obtain highly specific amplification products.

*Id.* Markoulatos also indicates that the "list of various factors that can influence the reaction is *by no means complete*." *Id.* (emphasis added). Indeed, Bustin similarly concludes that, "successful multiplexing is *never* trivial and *requires* careful consideration about the suitability of both chemistry and instrumentation." Bustin at 185, first column, second paragraph (emphasis added).

As discussed above, Bustin concludes that, "if quantification is the main aim, it is probably best to limit multiplexing to the detection of *two* or *three* transcripts." Bustin at 185, right col. second paragraph, while Backus only discloses the amplification of four targets, due to the difficulties associated with optimizing multiplex PCR.

Applicants also appreciated these problems, noting that the presence of many different primers leads to a high probability of primer dimer formation. As stated in the present specification, "[t]he presence of primer dimers dramatically reduces the efficiency of the reaction." Specification at page 6, lines 22-25. Applicants further indicated that, "[e]fficient co-amplification of multiple targets (multiplex PCR) is only possible when reaction conditions are chosen that allow all reactions to take place simultaneously and all reactions only minimally influence each other." *Id.* at lines 27-29.

In light of the disclosures of the Backus, Bustin and Markoulatus, discussed herein, the skilled artisan would have believed that a fair amount of luck and an enormous amount of optimization over a *long and incomplete* list of variables, conditions and parameters would be required order to develop a new multiplex PCR assay. The skilled artisan would have been further discouraged by the thought of attempting to design a multiplex PCR reaction capable of amplifying two or more different target nucleic acids present at *comparable* copy numbers because such experiments usually require tedious primer molar ratio determination experimentation.

Nevertheless, the Office Action continues to assert that "arguing that a method requires optimization is not evidence of a lack of reasonable expectation for success. A reasonable expectation of success does not require a guarantee of success." Office Action at page 23, first paragraph (emphasis added). Applicants respectfully disagree with this assertion.

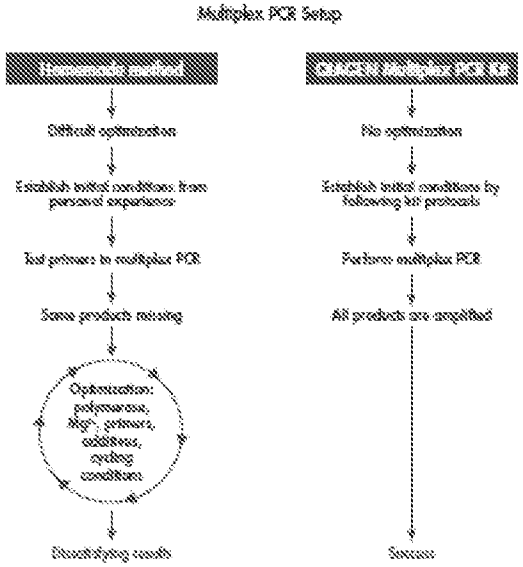
Applicants assert that it is precisely the *lack of necessary optimization* that renders the results obtained by the claimed methods unexpectedly superior to what would have been expected by one of skill in the art.

The claimed methods represent a rapid and efficient method that allows the skilled artisan to conduct a multiplex PCR assay in which two or more target sequences could be simultaneously amplified with *little or no* optimization work required. These unexpected and superior results are discussed in "New QIAGEN® Multiplex PCR Kit" *QIAGEN® News* 5:13-16 (November 2002) (hereinafter "QIAGEN® News," Exhibit A):

> The new QIAGEN® Multiplex PCR Kit is the first kit specifically developed for multiplex PCR. The simple multiplex master-mix solution *eliminates* the need for lengthy optimization procedures, such as adjusting the amounts of $Mg^{2+}$ and enzyme or even, as frequently required, adjusting primer concentrations. Now standard multiplex PCR applications are fast and easy to perform.

QIAGEN® News at page 13, first column, second paragraph (emphasis added). The Office Action even admits that "the content of the publication offered in [QIAGEN® News] and the results are impressive." Applicants have provided herewith further evidence demonstrating the methods that were performed to obtain the surprising and unexpected results set forth in QIAGEN® News.

Applicants compared the presently claimed methods with the difficult prior art optimization procedures associated with multiplex PCR in a cartoon in QIAGEN® News.



On page 15 of QIAGEN® News, Applicants describe experimental results using standard kit reagents of the presently claimed methods wherein 16 nucleic acid targets ranging from 99-995 bp are simultaneously and successfully amplified. The experimental design and methodology that was carried out to perform these experiments is detailed in the attached Declaration of Dr. Dirk Löffert (hereinafter "the Löffert Declaration").

*A. Standard Methods*

Reactions representative of what was available in the art at the time of filing the '976 application (hereinafter "standard methods") were carried out using the reaction components shown in Table 1 below. The standard methods utilized a conventional PCR buffer (AMPLI TAQ GOLD® buffer) and enzyme with a chemical hot-start, as described for example in Birch *et al.*, U.S. Patent No. 5,773,258. The amount of $MgCl_2$ was varied to determine the optimal concentration for multiplex PCR. *See* the Löffert Declaration at pages 3-4.

| **Table 1: Setup $MgCl_2$ titration with AMPLI TAQ GOLD® Buffer** | |
|---|---|
| Component | Final concentration |
| 10x AMPLI TAQ GOLD® buffer (C07612) | 1x |
| $MgCl_2$ (25 mM ABI; C07722) | 1.5 mM / 2.5 mM / 3.5 mM |
| AMPLI TAQ GOLD® (5U/µl; C04799) | 2.5 U |
| dNTP Mix (4mM) | 0.4 mM |
| Primermix 16 plex (2.5 µM each Primer) | 0.2 µM |
| Human genomic DNA | 20 ng |
| $H_2O$ | As needed |
| Total Volume | 50 µl |

*B. Methods of the Presently Claimed Invention*

The methods of the presently claimed invention on the other hand were carried out using the reaction components set forth below in Table 2. The QIAGEN® Multiplex PCR Master Mix contains a non-ionic, polymeric volume exclusion agent at an amount such that the final concentration of the volume exclusion agent in the total mixture is from 1 to 20 weight %. The QIAGEN® Multiplex PCR Master Mix also contains a thermostable hot start DNA polymerase. *See* the Löffert Declaration at page 4.

| **Table 2: Setup Multiplex PCR** | |
|---|---|
| Component | Final concentration |
| 2x QIAGEN Multiplex PCR Master Mix | 1x |
| Primermix 16 plex (2.5 µM each Primer; Table 4) | 0.2 µM |
| Human genomic DNA | 20 ng |
| $H_2O$ | As needed |
| Total Volume | 50 µl |

Table 4 below shows the primer sequences present in the Primermix 16 plex:

**Table 4: Primer 16-plex**

| Sequence | Name |
|---|---|
| GCC GAC AAA AGG AGA TCT GTG AGA A | ckit-for |
| GGC AAT GAC ATA CCA AAG GCT GGT A | ckit-rev |
| GCA CTG ATG GGC ACT GGA AAA CAT | PRPE3-for |
| GGA GCC AGA GGT ATC CAG GCA A | PRPE3-rev |
| TCT TCA ACC TCG CTG TGG CTG A | AGTRII3-for |
| ATC TTC AGG ACT TGG TCA CGG GTT | AGTRII3-rev |
| GCA CAA GGT CCC AGC ATC ATT GAT | mb1-for |
| CCG CGC AGA ACA GGA GGA TGA T | mb1-rev |
| CCT ATC TTC CTG CTG CTG GAC AA | B29E4-for |
| GGA GAG GGA TGG AGA TCA GAG TGT TA | B29E5-rev |
| TTT CCA GAC TTC CTG AGC CCT CAT | CD19E12-for |
| GCA TAC AGG ATT CCT CTC ATA TCC TCA T | CD19E13-rev |
| TGC CAT CCT CTT GGT GCT GGT CT | CD40E7-for |
| CAG CAG TGT TGG AGC CAG GAA GAT | CD40E9-rev |
| GCTGTTTGATGTCCTGCACGAG | ERCC1-for |
| GCCTGGCCTGGGAGGACGATT | ERCC1-rev |
| GAAGTTGTACAGGCCCAGTGTAGGAA | IL17F-for |
| CTTCTCCAACTGGAAAGAAACAGAGC | IL17F-rev |
| CTGTGAGCAGCTAGTGGTGGCTTC | Aqua-for |
| AACCAGTTGCATCATTCCCAGAAC | Aqua-rev |
| GGACTGCATTACAACAAATTCGGACAC | IL4P-for |
| CGTTACACCAGATTGTCAGTCACTTGG | IL4P-rev |
| GCTTGAGCAACCTGGCTAAGATAGAGG | CD59-for |
| GAGTTAGCAGGAGGCTGGATGCAGATG | CD59-rev |
| AGTGTGGGGTGCTAAACAGATCTCA | CAS10-for |
| AACCAAGGTGCAAAACAGTCTGCTA | CAS10-rev |
| CTTTTGGGAGTGTGGAAGTCCATAA | CD38-for |
| GGTGGGATCCTGGCATAAGTCTC | CD38-rev |
| CAACGTCTGCACTCTCGTGAGGG | ELA-for |
| CGGAGCGTTGGATGATAGAGTCGAT | ELA-rev |
| TGTCTGCAGTAGAGGTGGAGATCCAT | CD14-for |
| GCATCTCGGAGCGCTAGGGTTT | CD14-rev |

For the methods carried out under the presently claimed invention, the difference between the lowest copy number and highest copy number was less than 10-fold. The standard methods and Multiplex PCR reactions of the presently claimed invention were performed using the thermal cycling conditions given in Table 3 below. *See* the Löffert Declaration at pages 5-6.

| **Table 3: Cycling Protocol** | |
|---|---|
| Initial activation step | For QIAGEN® Multiplex Master Mix: 95°C, 15 min / For AMPLI TAQ GOLD®: 95°C, 10 min |
| Denaturation | 94°C 30 sec |
| Annealing | 61°C 90 sec |
| Extension | 72°C 90 sec |
| Number of cycles | 35 x |
| Final extension | 68°C 15 min |

As noted in Table 3, each of the 35 cycles comprised heating the reaction mixture to denature the strands, priming the denature strands by cooling to a second temperature, and forming primer extension products. *See id.* at page 6.

10 µl of each PCR reaction described in Tables 1-3 was then analyzed on an agarose gel stained with ethidium bromide to detect the primer extension products. The results of the gel analysis are provided below in Figure 1A of QIAGEN® News. *Id.*

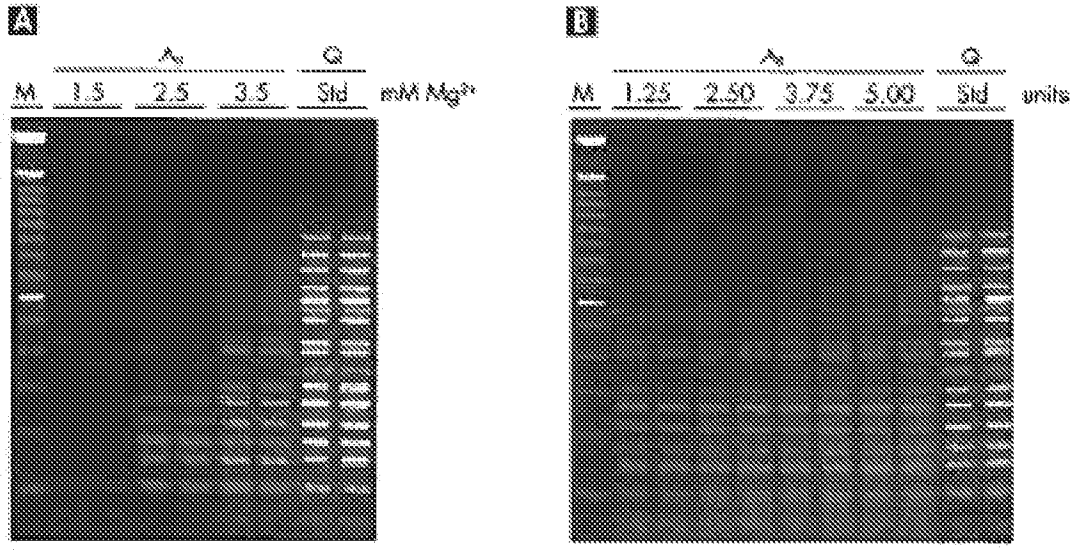



Figure 1 Multiplex PCR of 16 targets (99-955 bp) was carried out for 35 cycles using standard conditions (Std) for the QIAGEN Multiplex PCR Kit (Q) without further optimization or using a variety of conditions with a hot-start DNA polymerase from Supplier A (A). A Comparison using 2.5 units/50 µl reaction of the hot start DNA polymerase from Supplier A and with the indicated $Mg^{2+}$ concentrations. B Comparison using the optimized $Mg^{2+}$ concentration (3.5 mM) for the hot start DNA polymerase from Supplier A and the indicated amounts of enzyme per 50 µl reaction. M: markers.

As shown in Figure 1A, varying magnesium ion concentration (e.g., 1.5, 2.5, 3.5 mM) in the standard methods did not result in the successful co-amplification of the 16 targets in detectable quantities (see lanes 2-7). In contrast, using the methods of the presently claimed invention, successful co-amplification was achieved **in the first attempt** (see lanes 8 and 9 "Q"). *See id.* at page 7.

The methods described above were repeated utilizing a fixed amount of $MgCl_2$ (3.5 mM), and varying the amount of AMPLI TAQ GOLD® for the standard methods (e.g., 1.25, 2.5, 3.75, 5 Units). The reaction components are set forth in Tables 5 (standard methods) and 6 (methods of the presently claimed invention) below.

| **Table 5: Setup AMPLI TAQ GOLD® titration with AMPLI TAQ GOLD® Buffer** | |
|---|---|
| Component | Final concentration |
| 10 x AMPLI TAQ GOLD® Buffer (D01345) | 1x |
| $MgCl_2$ (25 mM ABI; D00424) | 3.5 mM |
| AMPLI TAQ GOLD® (5U/µl; CO4799) | 1.25 U / 2.5 U / 3.75 U / 5 U |
| dNTP Mix (4mM) | 0.4 mM |
| Primermix 16 plex (2.5 µM each Primer) | 0.2 µM |
| Human genomic DNA | 20 ng |

| | |
|---|---|
| $H_2O$ | As needed |
| Total Volume | 50 µl |

| **Table 6: Setup QIAGEN® Multiplex PCR MM** | |
|---|---|
| Component | Final concentration |
| 2x QIAGEN Multiplex PCR Master Mix | 1x |
| Primermix 16 plex (2,5 µM each Primer; Table 4 above) | 0.2 µM |
| Human genomic DNA | 20 ng |
| $H_2O$ | As needed |
| Total Volume | 50 µl |

PCR was performed using the thermal cycling conditions given in Table 7.

| **Table 7: Cycling Protocol** | |
|---|---|
| Initial activation step | For Qiagen Multiplex Master Mix: 95°C 15 min / For Ampli Taq Gold 10 min |
| Denaturation | 94°C 30 sec |
| Annealing | 61°C 90 sec |
| Extension | 72°C 90 sec |
| Number of cycles | 35 x |
| Final extension | 72°C 10 min |

10 µl of each PCR reaction described in Tables 5-7 was analyzed on an agarose gel stained with ethidium bromide. The results are shown in Figure 1B of QIAGEN® News.

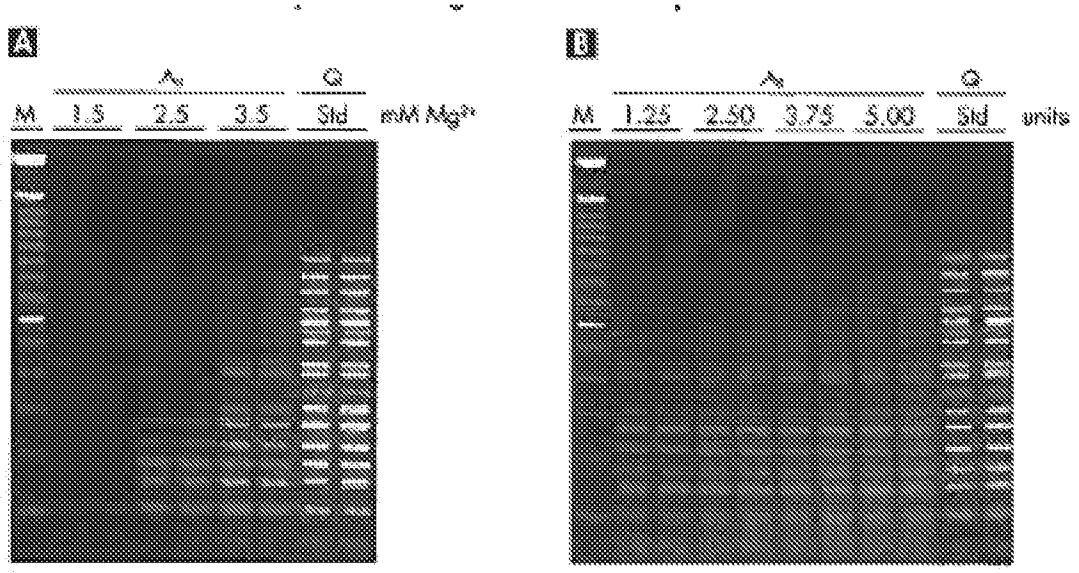



Figure 1 Multiplex PCR of 16 targets (99-955 bp) was carried out for 35 cycles using standard conditions (Std) for the QIAGEN Multiplex PCR Kit (Q) without further optimization or using a variety of conditions with a hot-start DNA polymerase from Supplier A (A). A Comparison using 2.5 units/50 µl reaction of the hot start DNA polymerase from Supplier A and with the indicated $Mg^{2+}$ concentrations. B Comparison using the optimized $Mg^{2+}$ concentration (3.5 mM) for the hot start DNA polymerase from Supplier A and the indicated amounts of enzyme per 50 µl reaction. M: markers.

As shown in lanes 2-9 of Figure 1B, optimization of the enzyme concentration with ostensible "optimized" magnesium ion concentration (see above) also failed to allow the standard methods to successfully coamplify the 16 targets in detectable quantities. In contrast, the methodology of the presently claimed invention, the results of which are represented in lanes 10-11 of Figure 1B, allowed for successful co-amplification **in the first attempt**. *See* the Löffert Declaration at page 9.

As opposed to the "tedious" standard methods which "require extensive optimization" often leading to "disappointing" results (*see* QIAGEN® News, p. 14, left col.), the presently claimed methods "eliminate the need for lengthy optimization procedures" and are "fast and easy to perform." (*See* QIAGEN® News, p. 13, left col.). Indeed, the presently claimed methods require "no optimization" (*see* QIAGEN® News) and "tedious optimization procedures are virtually eliminated." *See* "Highly Efficient Multiplex PCR Using Novel Reaction Chemistry," Agilent Technologies ©2003 at page. 4, left column. ("Engel," Exhibit C). *See* the Löffert Declaration at pages 9-10.

Applicants submit that those of ordinary skill in the art would have determined that in order to obtain results similar to those of the presently claimed invention, substantial

optimization of standard methods would have been required, with no guaranty and no reasonable expectation of arriving at the surprising and unexpected results that are shown in lanes 8/9 and 10/11 of Figures 1A and 1B, respectively, of QIAGEN® News, described above. Thus, the presently claimed methods clearly display unexpected and surprising results, as compared to standard methodology known at the time of filing the present application. *See* the Löffert Declaration at page 10.

Based on at least the arguments set forth above, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

## II. The Rejection of Claims 12-15, Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 12-15 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Backus in view of Bustin and Birch and further in view of Reed *et al.* U.S. Patent No. 5,459,038 (hereinafter "Reed") and Demke *et al.*, *Biotechniques 12*:333-334 (1992) (hereinafter "Demke"). Applicants respectfully traverse this rejection.

According to the Office Action, Backus, as modified by Bustin and Birch, allegedly disclose the presently claimed invention as set forth above. However, the Office Action concedes that these references do not disclose the use of dextran as a volume exclusion agent. The Office Action attempts to cure this deficiency with the disclosures of Reed and Demke. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to have extended the method of Backus to include dextran as discussed in Reed and Demke to achieve efficient amplification with higher sensitivity and specificity. Applicants respectfully disagree with these contentions and conclusions.

As set forth above and in previous argumentation, Applicants submit that the Office Action has not set forth a proper *prima facie* case of obviousness, as there would not have been a reasonable expectation of success of modifying the disclosure of Backus with that of Bustin and Birch. In addition, even if a *prima facie* case of obviousness was established, the unexpected results described herein clearly rebut this showing.

Applicants submit that these deficiencies are not cured by the disclosures of Reed and Demke, and hence, none of the cited references, alone or in combination, disclose this presently

claimed invention. In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

## III. The Rejection of Claim 25, Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 25 is rejected under 35 U.S.C. 103(a) as allegedly obvious over Backus in view of Bustin and Birch and further in view of Ivanov *et al.*, U.S. Patent No. 6,183,998 (hereinafter "Ivanov"). Applicants respectfully traverse this rejection.

According to the Office Action, Backus, as modified by Bustin and Birch, allegedly disclose the presently claimed invention as set forth above. However, the Office Action concedes that these references do not disclose a chemically modified DNA polymerase. The Office Action attempts to cure this deficiency with the disclosure of Ivanov, arguing that Ivanov discloses reversible modification of DNA polymerases through reaction with an aldehyde. Applicants respectfully disagree with these contentions and conclusions.

As set forth above and previously argued, Applicants submit that the Office Action has not set forth a proper *prima facie* case of obviousness, as there would not have been a reasonable expectation of success of modifying the disclosure of Backus with that of Bustin and Birch. In addition, even if a *prima facie* case of obviousness was established, the unexpected results described herein clearly rebut this showing.

Applicants submit that these deficiencies are not cured by the disclosure of Ivanov, and hence, none of the cited references, alone or in combination, disclose this presently claimed invention. In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

## IV. The Rejection of Claims 26-27, Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 26-27 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Backus in view of Bustin and Birch and further in view of Mansfield *et al.*, *Molecular Cellular Probes* 9:145-156 (1995) (hereinafter "Mansfield"). Applicants respectfully traverse this rejection.

According to the Office Action, Backus, as modified by Bustin and Birch, allegedly disclose the presently claimed invention as set forth above. However, the Office Action concedes that these references do not disclose that one of the primers is labeled with a specific binding moiety. The Office Action attempts to cure this deficiency with the disclosure of Mansfield, arguing that Mansfield discloses a variety of primer labeling techniques. Applicants respectfully disagree with these contentions and conclusions.

As set forth above and previously argued, Applicants submit that the Office Action has not set forth a proper *prima facie* case of obviousness, as there would not have been a reasonable expectation of success of modifying the disclosure of Backus with that of Bustin and Birch. In addition, even if a *prima facie* case of obviousness was established, the unexpected results described herein clearly rebut this showing.

Applicants submit that these deficiencies are not cured by the disclosure of Mansfield, and hence, none of the cited references, alone or in combination, disclose this presently claimed invention. In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

## V. The Rejection of Claims 30-36, Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 30-36 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Backus in view of Bustin and Birch and further in view of Groendahl *et al., J. Clin. Micro. 37*:1-7 (1999) (hereinafter "Groendahl"). Applicants respectfully traverse this rejection.

According to the Office Action, Backus, as modified by Bustin and Birch, allegedly disclose the presently claimed invention as set forth above. However, the Office Action concedes that these references do not disclose the simultaneous amplification of six or eight targets. The Office Action attempts to cure this deficiency with the disclosure of Grondahl, arguing that Grondahl discloses coamplifying six or eight different target nucleic acids. Applicants respectfully disagree with these contentions and conclusions.

As set forth above and previously argued, Applicants submit that the Office Action has not set forth a proper *prima facie* case of obviousness, as there would not have been a reasonable expectation of success of modifying the disclosure of Backus with that of Bustin and Birch. In

addition, even if a *prima facie* case of obviousness was established, the unexpected results described herein rebut this showing.

Applicants submit that these deficiencies are not cured by the disclosure of Grondahl, as Grondahl does not disclose that the maximum difference between the lowest and highest copy number is 10-fold, as recited in the presently claimed invention. Hence, none of the cited references, alone or in combination, disclose this presently claimed invention. In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

## VI. The Rejection of Claims 30-37, Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 30-37 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Backus in view of Bustin and Birch and further in view of Henegariu *et al.*, *Biotechniques 23*:504-511 (1997) (hereinafter "Henegariu"). Applicants respectfully traverse this rejection.

According to the Office Action Backus, as modified by Bustin and Birch, allegedly disclose the presently claimed invention as set forth above. However, the Office Action concedes that these references do not disclose the simultaneous amplification of six or eight targets. The Office Action attempts to cure this deficiency with the disclosure of Henegariu, arguing that Henegariu discloses coamplifying six or eight different target nucleic acids. Applicants respectfully disagree with these contentions and conclusions.

As set forth above and previously argued, Applicants submit that the Office Action has not set forth a proper *prima facie* case of obviousness, as there would not have been a reasonable expectation of success of modifying the disclosure of Backus with that of Bustin and Birch. In addition, even if a *prima facie* case of obviousness was established, the unexpected results described herein rebut this showing.

Applicants submit that these deficiencies are not cured by the disclosure of Henegariu, as Henegariu does not disclose the presently claimed invention. Hence, none of the cited references, alone or in combination, disclose this presently claimed invention. In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

## VII. Conclusion

Applicants believe that the claims are in condition for allowance and respectfully request allowance thereof. The Examiner is invited to telephone the undersigned if that would be helpful in resolving any issues.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-5071.

Respectfully submitted,

**Date:** **April 15, 2011**

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